REMARKS

Claims 1-88 are pending in the application. Claims 43, 54, 67-69, and 77-88 are withdrawn from consideration and Claims 1-42, 44-53, 55-66, and 70-76 have been examined. Claims 1-42, 44-53, 55-66, and 70-76 stand rejected. Claims 1, 21, 22, 44, 63, 65, and 70 have been amended. No new matter has been added. Applicants respectfully request reconsideration and allowance of Claims 1-42, 44-53, 55-66, and 70-76.

The Rejection of Claims Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,741,899 (Capon et al.). According to the Examiner, Capon et al. provides an enabling disclosure for making and using the vectors and cells for obtaining drug-induced proliferation of primary cells. Applicants respectfully disagree.

1. Claims 1-43, 59-66, and 70-76

Claims 1, 21, 22, 63, 65, and 70, from which Claims 2-20, 23-43, 59-62, 64, 66, and 71-76 depend, have been amended to clarify that the cells are exposed to a concentration of the drug effective to induce association of two or more fusion proteins. Support for this amendment is found in the specification, for example, at page 3, lines 2-5 and page 7, lines 11-14. For the following reasons and the reasons already of record in the Amendment and Response to Paper No. 17, filed February 11, 2004, and in the Amendment and Response to Non-Final Office Action, filed November 17, 2004, applicants submit that Capon et al. does not provide an enabling disclosure of the claimed invention because undue experimentation would be required for one of skill in the art to obtain the claimed primary mammalian cells or to practice the claimed methods of making or using these cells.

Capon et al. describes placing CPR-expressing $CD8^+$ T cells in "culture dishes coated with saturating concentrations of either OKT4A, anti-human Fc Mab, gp120, gp160-expressing

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cells, gp41/gp120-expressing cells, HIV-1 infected cells or FK1012" (Col. 42, lines 61-64). The Inventor's Declaration submitted herewith (hereinafter "Third Blau Declaration") provides further evidence that the method described in Capon et al. would not lead to drug-induced proliferation of primary mammalian cells, as described below (see Third Blau Declaration, paragraphs 5-9).

Saturating concentrations of a bivalent drug such as FK1012 inhibit growth by occupying all of the binding sites of its receptor and thereby preventing dimerization (see Third Blau Declaration, paragraph 6). For example, human growth hormone (hGH) is a bivalent molecule with two separate sites for binding to the extracellular domain of the human growth hormone receptor (hGHbp) (Fuh et al. (1992) *Science* 256:1677-80, page 1678, Col. 1; Fig. 1; of record). As stated in Fuh et al., "[a]t high concentrations, hGH saturates the receptor through site 1 interactions and acts as an antagonist" (Fuh et al. (1992) *Science* 256:1677-80, page 1678, Col. 2; Fig. 1).

The same effect is observed with saturating concentrations of FK1012 (Second Blau Declaration, paragraph 7). Proliferation of Ba/F3 cells expressing a chimeric protein containing an intracellular signaling domain linked to a FKBP domain in response to the FKBP-binding drug FK1012 is concentration-dependent, and at higher concentrations of the drug less proliferation is observed (Blau et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:3076-81, page 3078, Col. 1; of record). Moreover, experimental results obtained in Dr. Blau's laboratory on January 2, 1997, show that saturating concentrations of two FKBP-binding drugs (FK1012 and AP1510) completely inhibit proliferation of cells expressing a similar fusion protein that contains three copies of an FKBP domain linked to an intracellular signaling domain, similar to the chimeric proteins described in Capon et al. (Third Blau Declaration, paragraph 7, Table 1, Figures 1A and 1B). As pointed out by Dr. Blau, the concentration of drug required to saturate

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the binding sites of a drug-binding domain(s) in a particular fusion protein varies depending on the level of expression of the fusion protein inside the cell (Third Blau Declaration, paragraph 8). One of skill in the art could readily derive suitable drug concentrations that are effective to induce the association of two or more fusion proteins, thereby leading to proliferation of cells containing the fusion protein (Third Blau Declaration, paragraph 8).

Because Capon et al. teaches the use of saturating concentrations of FK1012, a person of skill in the art reading Capon et al. would not be able to practice the claimed methods following the teaching of Capon et al. (Third Blau Declaration, paragraph 9). Therefore, applicants submit that Capon et al. does not anticipate the invention of Claims 1-43, 59-66, and 70-76. Nor does Capon et al. render obvious the claimed invention; in fact, Capon et al. teaches away from the claimed invention by specifying the use of saturating concentrations of a drug, which would inhibit cell proliferation. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

2. Claims 44-53 and 55-58

Claim 44, from which Claims 45-53 and 55-58 depend, has been amended to recite that the drug-binding domain comprises at least one amino acid change compared to the most prevalent naturally-occurring amino acid sequence. Support for this amendment is found in the specification, for example, at page 17, line 12, to page 19, line 18. For example, Table 1 in the specification describes illustrative mutations in FKBP domains. Applicants respectfully submit that Capon et al. neither describes nor suggests fusion proteins containing drug-binding domains that have at least one amino acid change compared to a corresponding naturally-occurring amino acid sequence. Therefore, applicants submit that Capon et al. does not anticipate or render obvious the invention of Claims 44-53 and 55-58. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

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CONCLUSION

In view of the foregoing amendments and remarks, Claims 1-42, 44-53, 55-66, and 70-76 are believed to be in condition for allowance. If any issues remain that can be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1783.

Respectfully submitted,

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Karen Blöchlinger, Ph.D.
Registration No. 41,395
Direct Dial No. 206.695.1783

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: 7/7/05 Carole Julyan

KBB:cj

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	C.A. Blau et al.	Attorney Docket No.:	UWOTL115624
Application No.:	09/582,916	Group Art Unit:	1632
Filed:	October 2, 2000	Examiner:	A.M.S. Wehbe

Title: METHODS OF CONTROLLING CELL DIFFERENTIATION AND GROWTH USING A FUSION PROTEIN AND A DRUG

INVENTOR'S DECLARATION UNDER 37 C.F.R. § 1.132

TO THE COMMISSIONER FOR PATENTS:

I, Dr. Carl Anthony Blau, declare as follows:

1. I am a co-inventor named in the above-identified patent application and I am familiar with the subject matter of this application.

2. My educational and work background are as described in my previous declaration filed on November 17, 2004.

3. It is my understanding that U.S. Patent No. 5,741,899 (Capon et al.) has been cited as a prior art reference in the above-identified application.

4. The methods and cells claimed in this application, as amended, are directed to primary mammalian cells—such as hematopoietic stem cells—containing a construct encoding a fusion protein comprising at least one signaling domain and at least one drug-binding domain, wherein exposure to a drug of primary cells transduced with this construct reversibly induces growth, proliferation, or differentiation of the cells. Capon et al. does not provide an enabling description that would permit one skilled in the art to make and use primary mammalian cells (such as primary hematopoietic stem cells) containing a construct encoding a fusion protein comprising at least one signaling domain and at least one drug-binding domain.

5. Capon et al. does not provide an enabling description of methods of expanding primary mammalian cells (for example, primary hematopoietic stem cells) or methods of treating

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a hematopoietic disease or condition by exposing cells containing a construct coding for a fusion protein comprising at least one signaling domain and at least one drug-binding domain to the drug. Capon et al. describes placing CPR-expressing $CD8^+$ T cells in "culture dishes coated with saturating concentrations of either OKT4A, anti-human Fc Mab, gp120, gp160-expressing cells, gp41/gp120-expressing cells, HIV-1 infected cells or FK1012" (Col. 42, lines 61-64). However, the use of "saturating concentrations" of FK1012 would not result in proliferation because saturating concentrations of FK1012 inhibit growth by occupying all of the FKBP sites and thereby prevent dimerization, as further described below.

6. FK1012 is a bivalent drug that induces dimerization of two FKBP domains. It has been shown that high concentrations of a bivalent drug prevent dimerization of a receptor for that drug. For example, human growth hormone (hGH) is a bivalent molecule with two separate sites (site 1 and site 2) for binding to the extracellular domain of the human growth hormone receptor (hGHbp) (Fuh et al. (1992) *Science* 256:1677-80, page 1678, Col. 1; Fig. 1; of record). As stated in Fuh et al., "[a]t high concentrations, hGH saturates the receptor through site 1 interactions and acts as an antagonist" (Fuh et al. (1992) *Science* 256:1677-80, page 1678, Col. 2; Fig. 1).

7. The same effect is observed with saturating concentrations of FK1012, as described in my declaration filed on November 17, 2004. Further evidence is provided by the following experimental results obtained in my laboratory on January 2, 1997, which show that saturating concentrations of FK1012 inhibit proliferation of cells expressing a chimeric protein that is analogous to those described in Capon et al. A clone of Ba/F3 cells expressing the chimeric protein F3FLK2, which contains three copies of an FKBP domain linked to the Flk-2 intracellular signaling domain (also known as Flt-3), was exposed to increasing concentrations of two drugs, FK1012 and AP1510. Cell proliferation was measured using a previously described assay (Blau et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:3076-81, page 3077, Col. 1-2). The

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amount of cell proliferation was compared to the proliferation obtained in the presence of IL-3-containing medium (WEHI-conditioned medium). As shown in Table 1 and Figures 1A and 1B, F3FLK2-containing BA/F3 cells are capable of FK1012-dependent proliferation and AP1510-dependent proliferation in the absence of IL-3. The maximum amount of proliferation of this clone of F3FLK2-expressing cells was obtained at about 1 nM of FK1012 and at about 10 nM of AP1510. However, concentrations of FK1012 or AP1510 above 10 nM were found to inhibit cell proliferation and at concentrations above about 100 nM FK1012 (Table 1, Figure 1A) or AP1410 (Table 1, Figure 1B), no cell growth was observed. These results unequivocally demonstrate that drug concentrations sufficient to saturate all of the FKBP sites completely prevent drug-induced cell proliferation, similar to the results described for hGH. Because the mechanisms of dimerization of a receptor for a bivalent drug is the same in primary cells, saturating concentrations of a bivalent drug would also prevent drug-induced proliferation of primary mammalian cells.

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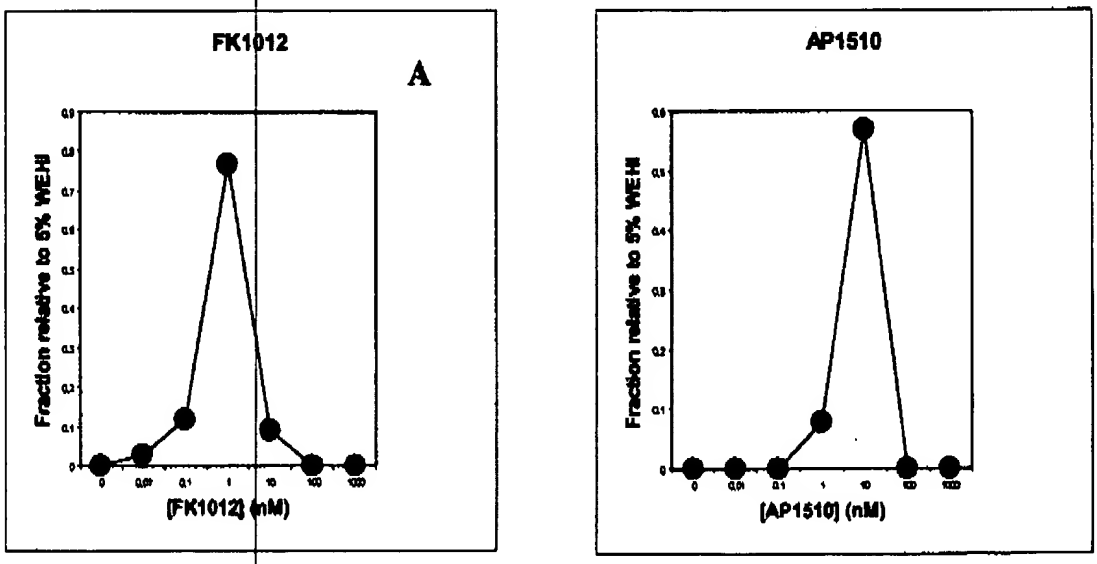
Table 1. Effect of Increasing Concentrations of FK1012 and AP1510 on Cell Proliferation in F3FLK2-Containing Ba/F3 Cells

Concentration of Drug (nM)		Growth Relative to 1% WEHI
FK1012	0	0
	0.01	0.027636
	0.1	0.118731
	1	0.765609
	10	0.91095
	100	0
	1000	0
AP1510	0	0
	0.01	0
	0.1	0
	1	0.078813
	10	0.568066
	100	0
	1000	0

FIGURE 1.



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8. It should be noted that the concentration of drug needed to saturate the drug-binding site(s) in a fusion protein depends on the level of expression of the fusion protein. Thus, if the level of expression of the fusion protein is high, the concentration of drug need to saturate the receptors would be correspondingly higher. It is therefore not surprising that 1000 nM of the drug was sufficient to significantly or completely inhibit growth of some but not all Ba/F3 cell clones, as described in Jin et al. (1998) *Blood* 91:890-7, and Zeng et al. (2001) *Blood* 98:328-34).

9. Because Capon et al. teaches the use of saturating concentrations of FK1012 (i.e., inhibitory concentrations of FK1012), a person of skill in the art following the teaching of Capon et al. would not be able to practice the methods of the present application of expanding primary mammalian cells—including hematopoietic stem cells—or methods of treating a hematopoietic disease or condition by exposing cells containing a construct coding for a fusion protein comprising at least one signaling domain and at least one drug-binding domain to a concentration of a drug effective to induce association of two or more fusion proteins, as described and claimed in the above-identified patent application.

10. All statements made herein and of my own knowledge are true, and all statements made on information and belief are believed to be true; and further, these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such

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willful, false statements may jeopardize the validity of the above-identified application or any patent issued thereon.

Respectfully submitted,

Dated: 7/6/05

C. A. Blau

Dr. C.A. Blau

KBB:cj

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